Current Approaches to Diagnosis And Management of Insect Sting Allergy

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DISCLOSURES

Speakers Bureau
- Genentech / Novartis
- Mylan / Dey

Research / Clinical Trials
- Genentech / Novartis
- Siemens

Consultant
- Stallergenes
- Sanofi-Aventis

Venom Immunotherapy: Who Needs It?

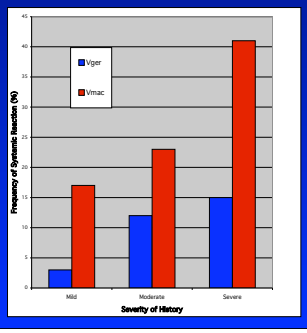
- Positive venom skin test or serum test, **AND**
- History of systemic reaction to sting
  - Life-threatening
  - Moderate throat/airway symptoms or dizziness
  - Cutaneous systemic ?
  - Large local ?

Assessment of Risk in Patients with Insect Sting Allergy

- History (severity and pattern of reaction)
- Venom-specific IgE by skin or serum tests
- Natural History / Progression
- Baseline serum tryptase
- Quality of life
- Age / Medical condition

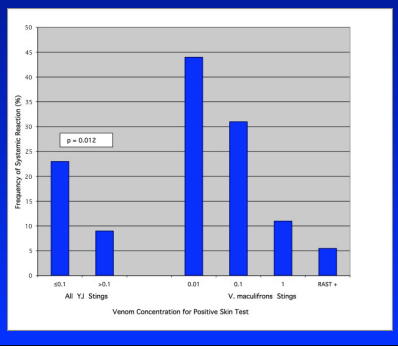
Risk of Systemic Reaction Depends on Severity of Previous Reactions and Insect Species

(Golden et al - JACI 2006)



Risk of Sting Reaction Related to Venom Skin Test

(Golden et al - JACI 2006)



Negative Venom Skin Tests with History of Sting Anaphylaxis

- Refractory (anergic) period
- Variability of venom skin tests
- Mast Cell Disorder
- No longer allergic / Never was allergic ?

Negative skin test and serum IgE

– 5% chance of systemic reaction

Elevated Tryptase (Mastocytosis) and Insect Sting Anaphylaxis

- Elevated baseline serum tryptase in:
  – 5 -10% of patients with sting anaphylaxis
  – up to 25% of patients with hypotensive shock
- Elevated tryptase associated with:
  – more severe reactions to insect stings
  – more frequent systemic reactions during VIT
  – more frequent VIT treatment failure
  – more frequent relapse after stopping VIT

VIT in Patients with Mastocytosis

deOlana et al. JACI 2008;121:519

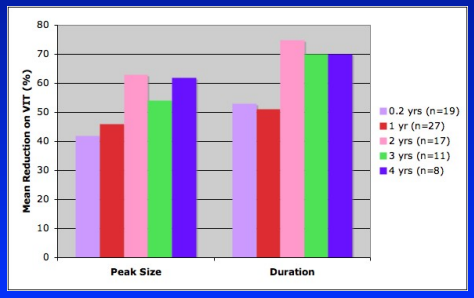
Male / Female	17 / 4
Vespid allergic / HB allergic	75% / 25%
Systemic reactions during VIT	6 (28%)
up-dosing	3 (14%)
maintenance	3 (14%)
Systemic reaction to sting (n=12)	3 (25%)
Venom IgE pre/post VIT	4.1 / 1.2

Natural History of Insect Allergy: Risk Based on Severity of Previous Reactions

Previous Sting Reaction	Chance of Future Systemic Sting Reaction: Any	Severe
Life-threatening	50 - 75%	30%
Moderate Systemic	30 - 50%	10%
Cutaneous Systemic		
– child	1 - 10%	<3%
– adult	10 - 20%	<5%
Large Local	5 - 10%	2%

Mean Reduction of Large Local Reactions During Maintenance Venom Immunotherapy

(Golden et al. JACI 2009;123:1386)



Controlled Trial of Venom Immunotherapy

(Hunt et al, NEJM 1978)

Treatment	Stung	Systemic	(%)
Venom (n=19)	18	1	(5%)*
W B E (n=20)	11	7	(64%)
Placebo (n=20)	12	7	(58%)

* after crossover, total 1/55 = 2% on VIT (p<0.01)

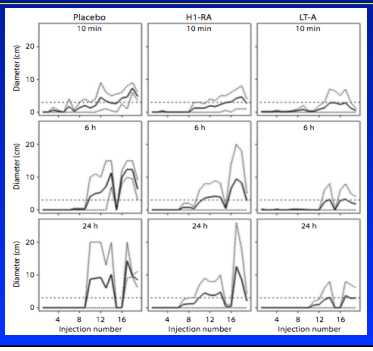
Mechanisms of Venom Immunotherapy

1. Dreschler K, Bratke K, Petermann S, Bier A, Thamm P, Kuepper M, et al. **Impact of immunotherapy on blood dendritic cells in patients with Hymenoptera venom allergy.** J Allergy Clin Immunol 2011; 127:487-94.
2. Jutel M, Akdis CA. Immunological mechanisms of allergen-specific immunotherapy. Allergy 2011;66:725-32.
3. Kerstan A, Albert C, Klein D, Brocker EB, Trautmann A. Wasp venom immunotherapy induces activation and homing of CD4+CD25+ forkhead box protein 3-positive regulatory T cells controlling Th1 responses. J Allergy Clin Immunol 2011; 127:495-501.
4. Varga EM, Francis JN, Zach MS, Klunker S, Aberer W, Durham SR. Time course of serum inhibitory activity for facilitated allergen-IgE binding during bee venom immunotherapy in children. Clin Exp Allergy 2009; 39:1353-7.
5. Jutel M, Akdis M, Blaser K, Akdis CA. Are regulatory T cells the target of venom immunotherapy? Curr Opin Allergy Clin Immunol 2005; 5:365-9.

Pre-medication During Venom Immunotherapy

	Terfenadine	Placebo
Brockow et al (JACI 1997)		
Systemic during VIT	1/82 (1%)	6/39 (15%)
Large Local during VIT	20/80 (24%)	17/39 (45%)
Muller et al (JACI 2001)		
Systemic during VIT	5/24 (21%)	13/23 (56%)
Systemic to challenge sting	0/20	6/21 (28%)

Montelukast reduces Large Local Reactions to VIT (Wohrl S et al. Int. Arch Allergy Immunol 2007;144:137)



Safety of Initiating VIT at 1 mcg dose.

Roumana et al. JACI 2009.

TABLE II. Systemic reactions caused by rush and ultrarush VIT

Venom concentration	Dose (in µg)	Injections (no.)	Observed reactions (no.)	Injections causing reaction (%)
10 µg/mL	1 µg	730	0	0
	3-6 µg	1,460	25	1.7
100 µg/mL	10-50 µg	3,650	84	2.3
	>50 µg	2,190	110	5
Total		8,030	219	2.7

	Reactors to bee venom			Reactors to vespid venom		
Dose	Mild	Moderate	Severe	Mild	Moderate	Severe
3-6 µg	8	3	–	5	–	–
>6-50 µg	39	11	3	6	0	–
>50 µg	41	23	8	7	1	–
Patients*	71	31	9	18	1	0
Total†	83/428 (19.3%)			18/302 (5.9%)		
Mean RR	13.8%					

Venom Immunotherapy with a 50 µg Maintenance Dose in Children

Houliston 2011
- 85 children on HB-VIT
- 34 stung during VIT – 7 SR (21%)
- 44 stung after VIT – 6 SR (14%)

Konstantinou 2011
- 53 children (29 HB, 26 YJ)
- 2 SR to HB-VIT (dose increased to 100 µg)
- 10 stung (2 HB) during VIT (3.2 ±1.4 yrs)
  - 7 (3 HB) stung again 2 wks-2 yrs later
- 11 stung (5 HB) 3.5±2.9 yrs post-VIT

Problems During VIT

- Large local reactions
- Systemic reactions
- Treatment failure
- Medications
- Pregnancy

Systemic Reactions During VIT

- Premedication
- Single venom
- Cluster VIT
- Rush VIT
- Omalizumab
- Increase dose

Dose Response of Venom Immunotherapy

(Rueff et al JACI 2001;108:1027-32.)

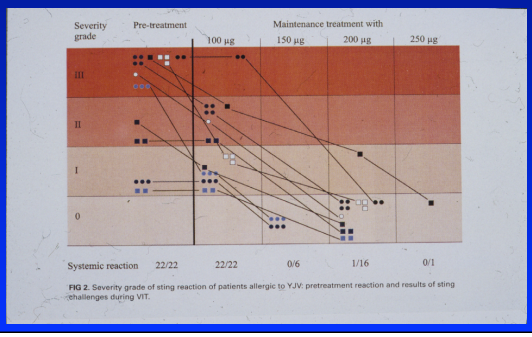


FIG 2. Severity grade of sting reaction of patients allergic to YJV: pretreatment reaction and results of sting challenges during VIT.

Rush VIT in Patients Having Systemic Reactions to VIT (Goldberg et al, Ann Allergy 2003;91:405)

Table 2. Rush Venom Immunotherapy Protocol*

Day	Venom concentration, • g/mL	Volume, mL	Dose, • g	Daily accumulative dose, • g
1	1	0.05	0.05	
	1	0.1	0.1	
	1	0.2	0.2	
	1	0.4	0.4	
	1	0.8	0.8	
	10	0.2	2	
	10	0.5	5	
	10	1.0	10	
	100	0.2	20	
	100	0.2	20	58.55
2	100	0.2	20	
	100	0.3	30	
	100	0.5	50	100
3	100	1.0	100	100

* There were 15-minute intervals between venom injections.

Omalizumab treatment in patients with severe anaphylactic reactions to VIT

Galera 09 (couldn't stop Xolair!)

Gomis 2008 (failure of Xolair)

Kontou-Fili 2008 (high dose Xolair in masto)

daSilva 2013 (rush HB in monoclonal MCAS)

5 other cases of successful rush VIT on Xolair, all stable off Xolair after 6-12 months.

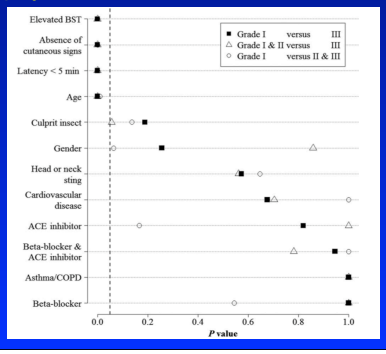
Predictors of severe systemic reactions in patients with insect allergy.

Rueff et al. EAACI Interest Group on Insect Allergy, JACI 2009;124:1047.

TABLE II. Distribution of the severity grade of systemic anaphylactic reactions (grade I/II or III/IV) after the index sting with respect to baseline parameters

Parameter		Grade I or II reaction (n 5 756)	Grade III or IV reaction (n 5 206)	P value
b-Blocker medication at the time of the index sting	Yes	34 (65.4%)	18 (34.6%)	.024
	No	722 (79.3%)	188 (20.7%)	
ACE inhibitor medication at the time of the index sting	Yes	24 (57.1%)	18 (42.9%)	.002
	No	732 (79.6%)	188 (20.4%)	
Any antihypertensive medication at the time of the index sting	Yes	61 (63.5%)	36 (36.5%)	<.001
	No	695 (80.4%)	170 (19.6%)	
Sex	Male	385 (73.6%)	138 (26.4%)	<.001
	Female	371 (84.5%)	68 (15.5%)	
One or more preceding, less severe systemic sting reactions before index sting	Yes	46 (48.4%)	49 (51.6%)	<.001
	No	710 (81.9%)	157 (18.1%)	
Insect responsible for index sting and associated allergic reaction	Bee	241 (83.4%)	48 (16.6%)	.016
	Vespid	515 (76.5%)	158 (23.5%)	
Age (y) at index sting according to median	<38	424 (86.2%)	68 (13.8%)	<.001
	• 38	332 (70.6%)	138 (29.4%)	

Factors correlating with the severity of anaphylaxis (Stoevesandt et al. JACI 2012)



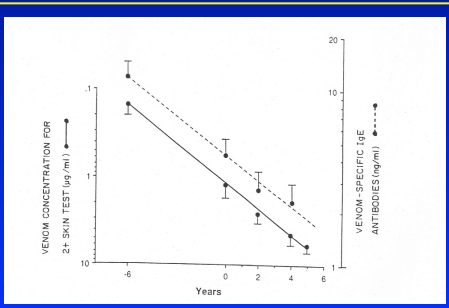
Maintenance VIT

- Maintenance interval
  - 4 wks, 6 wks, 8 wks (x 12-18 mo each)
  - 12 weeks (Goldberg 2001; Cavallucci 2010)
- Monitoring
  - Skin test
  - Specific serum IgE or IgG
  - Medications (β-blockers; ACE inhibitors)

Duration of VIT – When to Stop

- 5 years or 3 years?
- Time or testing?
- What do I test or evaluate?
  - Skin test?
  - Specific serum IgE or IgG?
  - Serum tryptase?
  - History?

Venom-IgE and Skin Test During and After Venom Immunotherapy



Extended Observations After Discontinuing Venom Immunotherapy

Golden et al. JACI 1998;101:298.

Years Since VIT	Patients Stung	Years On VIT	Years Off VIT	Systemic Reactions
Short Term	112	6 (5- 8)	3.1 (1- 4)	12/112 (10.7%)
Long Term	50	7 (5-17)	9.6 (5-13)	5/50 (10%)
Total	113	6.7 (5-17)	7.0 (1-13)	16/113 (14.2%)

Severity of Sting Reactions Before VIT and After Discontinuing VIT (n=89)

Sting Reaction	Before VIT	After VIT
Minimal	**0**	**6**
Gen. Urticaria angioedema (only)	**13**	**2**
Respiratory	**41**	**3**
Hypotension	**35**	**1**

Mean Duration of VIT = 6.5 years (5-9 years)
Mean Interval After VIT = 3.5 years (2-7 years)

Discontinuing Venom Immunotherapy: Caveats

- Extreme / Near-fatal reaction
- Systemic reaction during VIT (injection or sting)
- Mast cell disorder/elevated tryptase
- Honeybee allergy
- Age / Medical condition
- Quality of Life